event the examiner refuses to consider the drawings, the drawings and all references thereto will be canceled from the specification. Figures 9-11 have been cancelled.

Information Disclosure Statement

Enclosed are copies of the PTO Form 1449 filed on April 3, 2000 and the references listed therein which were not considered by the Examiner.

Restriction Requirement

The Examiner has divided the specification into four groups as follows:

Group I: Claims 1-5, 11-18, drawn to a vaccine, classified in class 424, subclass 230.1;

Group II: Claims 6-10, 19-22, drawn to a diagnostic test, classified in class 435, subclass 5;

Group III: Claims 23-25, drawn to an *in vivo* screening method for therapeutics, classified in class 424, subclass 9.2; and

Group IV: Claim 26, drawn to a method of screening risk factors, classified in class 435, subclass 6.

In a telephone conversation with the Examiner on November 30, 2000, applicants agreed to a restriction without traverse to Group II, claims 6-10 and 19-22, and applicants hereby affirm this election. Claims 1-5, 11-28, and 23-26 have been canceled.

Priority Benefit

Applicants only intended to claim priority to January 13, 1997. The examiner's acknowledgement of this claim is appreciated.

Claim Objections

Claims 8 and 20 were objected to as improper Markush claims. These have been amended to correct the errors. The examiner's careful review is appreciated.

Double Patenting

In the event both applications, this application and U.S.S.N. 08/781,296 are otherwise determined to be allowable, the assignee of both applications, the Oklahoma Medical Research Foundation, will file a Terminal Disclaimer.

Rejections under 35 U.S.C. 112

Claims 6-10 and 19-22 were rejected under 35 U.S.C. 112, second paragraph, as indefinite, and under 112, first paragraph, as not enabled. These rejections are respectfully traversed if applied to the amended claims.

Claims 8 and 21 have been amended to correct the Markush group, as noted above.

Claims 6-10 and 19-22 have been rejected apparently for use of the term "likelihood" and "at risk". Contrary to the statement that one would not know what this means, the terms are well known to those skilled in the art. Particularly in a case such as lupus, where there is a genetic component (same as in some types of cancer or heart disease), there are tests that can be performed to indicate if an individual is more likely than the average individual to develop a disorder, in this case, lupus. It is now well established that those individuals with elevated titers to Epstein-Barr virus are at greater risk of developing Burkitt's lymphoma and nasopharyngeal carcinoma (see page 2, first paragraph, and references cited therein).

Claims 7 and 20 were rejected on the basis that the claim is indefinite as to whether or not the same reagents are used with low levels of antibodies as with high levels of antibodies. Claims 7 and 20 have been amended to more clearly indicate that different assays are being referred to and to correct the Markush format.

Claims 6-10, and 19-22 were rejected as not enabled. The standard for enablement is whether or not one skilled in the art can make and use that which is claimed. The specification is fully enabling to one skilled in the art to collect patient samples and assay them as claimed, without undue experimentation. That is all that is required by the statute.

However, to facilitate prosecution, the autoimmune disease to be screened for has been limited to lupus.

The real basis of the rejection is that the examiner does not believe applicants' data. However, applicants are MD, Ph.D.s who are experts in the field of immunology, who routinely treat these types of patients, and the data in this application and preceeding applications has been published in numerous peer-reviewed journals and presentations. This work has been funded by NIH. In contrast, the examiner has provided no evidence of why the data would not be considered enabling to those skilled in the art, only made observations, unsupported by scientific literature or other confirmatory evidence. Referring to the prior art which did not identify the claimed peptides and saying that they failed to have made the same observations supports patentability; not negates it. The examiner's analysis therefore fails to meet the legal standard for non-enablement, as held repeatedly by the

Court of Appeals for the Federal Circuit and presented in the MPEP.

Rejections under 35 U.S.C. 102 and 103

Claims 6,7, 10, 19 and 20 were rejected under 35 U.S.C. 102 as disclosed by Rhodes, et al., 1985. J. Immunol. 134(1):211-216. Claims 8, 9, 21 and 22 were rejected under 35 U.S.C. 103 as obvious over Rhodes, et al. Claims 6-10 and 19-22 were rejected under 35 U.S.C. 102(b) as disclosed by, or under 103 as obvious over, Petersen, et al., 1990 Arthritis and Rheumatism 33(7):993-1000. These rejections are respectfully traversed.

The Claimed Invention

As defined by claim 6, applicants have provided the reagents, and data to support the conditions for measurement of, and course of development in patients of, antibodies elicited by initial infection with Epstein-Barr virus, which leads to development of lupus in susceptible individuals. Note that applications are claiming a test for increased liklihood; not certainty. The diagnostic test comprises:

(1) reagents which can be used to detect
levels of antibodies to Epstein-Barr virus,
indicators of Epstein-Barr infection of cells, or
levels of Epstein-Barr DNA or protein in a patient,

(2) control samples from individuals not at risk of developing an autoimmune disease, and

(3) means for determining the differences in levels of a patient and control samples to distinguish individuals at higher risk of developing an autoimmune disease from those at lower risk of developing an autoimmune disease.

A key element here is the identification of those individuals who are "not at risk".

None of the prior art has been able to provide this element. Therefore the prior art cannot disclose, nor anticipate, the claimed composition.

As discussed at page 13, about 95% of individuals are seroconverted for Epstein-Barr virus (EBV) - i.e., they have antibodies to EBV. Therefore, merely testing an individual for the presence of antibodies to EBV is not sufficient to identify someone who is, or is not, at risk of developing an autoimmune. Applicants' composition allows the identification of those individuals who have antibodies to certain peptides and are therefore at risk, and those who do not have antibodies to the same peptides (regardless of whether or not they have other anti-EBV antibodies), that are not at risk, and therefore useful as controls. See page 14, lines 3-20.

Rhodes

As noted by the examiner, Rhodes does not identify specific peptides. He only distinguishes between those individuals who have, or who do not have, antibodies to EBV, and who have, or do not have, an autoimmune disease. His own data establishes the lack of predictability of his system.

Sine Rhodes does not identify those who are "at risk" of developing, but only those with or without autoimmune disease, and with or without anti-EBV, he does not disclose the claimed composition, nor make it obvious. As the Court discussed in In re Fiers, merely have the plan to isolate something does not make obvious the specific molecule. In this case, Rhodes did not even

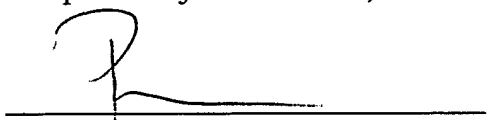
have the plan to identify peptides which do, or do not, induce autoimmunity. It is simply not part of the disclosure.

Petersen

Petersen is much the same. He compares the specificity of anti-EBV antibodies in Rheumatoid arthritis and normal individuals, and concludes that the populations are different. Based on his data, one would screen populations for reactivity with two non-glycine-alanine peptides and to three non-glycine-alanine peptides. He also notes that reactivity to other EBV peptides was basically the same in both groups. Based on his data, one would use approximately one-third of the EBNA-1 molecule (see page 994, col. 2) as a reagent to screen rheumatoid arthritis patients. One would not expect to see the same reactivity with RA patients as with SLE patients. Petersen therefore fails to disclose the claimed composition, or method of use, or make them obvious.

Allowance of claims 6-11 and 19-22, as amended, is earnestly solicited.

Respectfully submitted,



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CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this , along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: June 28, 2001

Patrea Pabst

APPENDIX: Claims marked to show amendments

6. (amended) A diagnostic test to predict the risk of developing lupus comprising

reagents which can be used to detect levels of antibodies to Epstein-Barr virus, indicators of Epstein-Barr infection of cells, or levels of Epstein-Barr DNA or protein in a patient, and

control samples from individuals not at risk of developing [an autoimmune disease] lupus, and

means for determining the differences in levels of a patient and control samples to distinguish individuals at higher risk of developing [an autoimmune disease] lupus from those at lower risk of developing [an autoimmune disease] lupus.

7. (amended) The diagnostic test of claim 6 wherein the reagents are used in assays selected from the group of assays based upon the relative presence of an antibody, assays based on cellular proliferation, assays based on molecular binding, assays based on cytokine production, assays based on skin reaction, [or] and assays based on cell surface antigen.

8. (amended) The diagnostic test of claim 6 wherein the reagents [are] used to detect antibodies to peptides from Epstein-Barr virus are selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPSC (SEQ ID NO:26), QKRPSCIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPPRRPPPGR

(SEQ ID NO:103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQPGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSFDDG (SEQ ID NO:49), PPWFPPMVEG (SEQ ID NO:50).

9. The diagnostic test of claim 8 comprising reagents for detection of antibodies to GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7).

10. The diagnostic test of claim 6 for testing patients identified with or at risk of developing systemic lupus erythematosus comprising control samples from individuals with systemic lupus erythematosus.

Please cancel claims 11-18.

19. (amended) A method for determining the likelihood that an individual has [an autoimmune disorder] <u>lupus</u> induced by Epstein-Barr virus, or is at risk for developing [such an autoimmune disorder] <u>lupus</u>, comprising

obtaining a sample from the individual to be tested,

mixing the sample with reagents which can be used to detect levels of antibodies to Epstein-Barr virus, indicators of Epstein-Barr infection of cells, or levels of Epstein-Barr DNA or protein in a patient,

analyzing the sample, and

comparing the analysis of the sample with results obtained with control samples from individuals not at risk of developing

[an autoimmune disease] lupus to determine if the differences in levels of the individual and control samples indicates the individual is at a higher risk of developing [an autoimmune disease] lupus than controls who are at lower risk of developing [an autoimmune disease] lupus.

20. (amended) The method of claim 19 wherein the reagents are used in assays selected from the group of assays based upon the relative presence of an antibody, assays based on cellular proliferation, assays based on molecular binding, assays based on cytokine production, assays based on skin reaction, [or] and assays based on cell surface antigen.

21. (amended) The method of claim 19 wherein the reagents [are] used to detect antibodies to peptides from Epstein-Barr virus are selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPSC (SEQ ID NO:26), QKRPSCIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPPRRPPPGR (SEQ ID NO:103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID

NO:46), PQPGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSFDDG (SEQ ID NO:49), PPWFPPMVEG (SEQ ID NO:50).

22. The method of claim 19 wherein the individual is tested for the presence of antibodies to GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7).

Please cancel claims 23-26.